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Toward Optimizing the Performance of Homogeneous L-Au-X Catalysts through Appropriate Matching of the Ligand (L) and Counterion (X^-)

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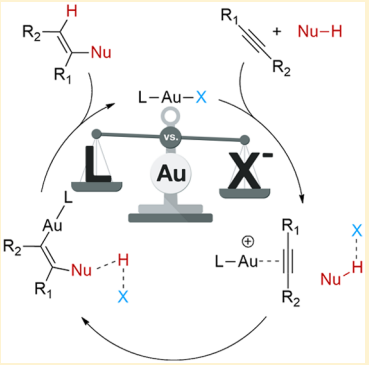
Supporting Information

ABSTRACT: The effects of the ligand (L) and counterion (X^-) are considered the two most important factors in homogeneous gold catalysis, but a rational understanding of their synergy/antagonism is still lacking. In this work, we synthesized a set of 16 gold complexes of the type L-Au-X that differ as follows: (i) L = PPh_3 (**L1**), $P(^tBu)_3$ (**L2**), tris(3,5-bis(trifluoromethyl)phenyl)phosphine (PArF, **L3**), and 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (NHC, **L4**), with the deliberate purpose of varying the electron withdrawing ability of the ligand, and (ii) X^- = BF_4^-, OTf^-, OTs^-, and TFA^-, which have various coordinating abilities, basicities, and hydrogen bond acceptor powers. All these catalysts were tested in two different model reactions: the cycloisomerization of *N*-(prop-2-ynyl)benzamide to 2-phenyl-5-vinylidene-2-oxazoline and the methoxylation of 3-hexyne. The main results are that the choice of the most efficient L-Au-X catalyst for a given process should not be made by evaluating the properties of L and X^- alone, but rather based on their best combination. For NHC-Au-X, the noncoordinating and weakly basic anions (such as BF_4^- and OTf^-) have been recognized as the best choice for the cycloisomerization of *N*-(prop-2-ynyl)benzamide. On the other side, the intermediate coordinating ability and basicity of OTs^- provide the best compromise for achieving an efficient methoxylation of 3-hexyne. A completely different trend is found in the case of complexes bearing phosphanes: OTs^- and TFA^- have been found to accelerate the cycloisomerization of *N*-(prop-2-ynyl)benzamide, and BF_4^- and OTf^- are suitable for the methoxylation of 3-hexyne. A possible explanation of the observed differences between phosphane and NHC ancillary ligands might be found in the higher affinity of the counterion (especially OTs^-) for the gold fragment for phosphane instead of NHC.



INTRODUCTION

In recent years, homogeneous gold catalysis has received considerable attention and represents a fast growing area of organic chemistry.[1] Most of these reactions can be classified as nucleophilic additions to a carbon−carbon unsaturated bond promoted by L-Au-X compounds (L = an ancillary ligand, and X^- = a counterion). In essentially all the proposed mechanisms, the gold metal fragment L-Au-X [inner sphere ion pair (ISIP)] acts as a Lewis acid coordinating unsatured hydrocarbons, i.e., alkyne, in the pre-equilibrium step [Scheme 1, intermediate **I**, outher sphere ion pairs (OSIP)] that subsequently undergoes nucleophilic attack by a nucleophile (Nu-H), with the formation of organogold intermediates (Scheme 1, intermediate **II**). The gold−carbon bonds in these intermediates are typically cleaved by a proton, protodeauration, to give the desired products and regenerate the catalyst (Scheme 1). In-depth kinetic and mechanistic studies of gold(I)-catalyzed nucleophilic addition to a carbon−carbon unsaturated bond have been appearing in the literature,[2] with a goal of understanding the ligand effects in the different steps of the catalytic cycle.[3] The ligand electronic structure, in particular its electron donating ability, modulates the acidic character of the metal fragment in the catalytic cycle and affects the stability of the postulated intermediates[4,5] (alkene/alkyne gold complexes,[6] vinyl gold compounds,[7] carbene gold complexes,[8] and more or less delocalized carbocationic[9] complexes).

On the other hand, the anion plays an important role in gold catalysis, influencing the catalytic activity,[10] the regioselectivity,[11] and even the stereoselectivity[12] of the process. Moreover, it has been well established that the structures of the catalyst[13] and the intermediates[14] are affected by the counterion.[6,15] Even if several experimental data concerning the "counterion effect" in gold catalysis have been published,[16] its rationalization is still far from being fully obtained, but the idea that coordination ability and basicity of the counterion may have a great impact on the catalytic performance of gold complexes is now accepted.[16] With respect to this topic, very recently, we[17,18] and others[19] studied the Au-catalyzed intermolecular methoxylation[20,21] of alkynes and proposed that the nucleophilic attack of methanol is assisted

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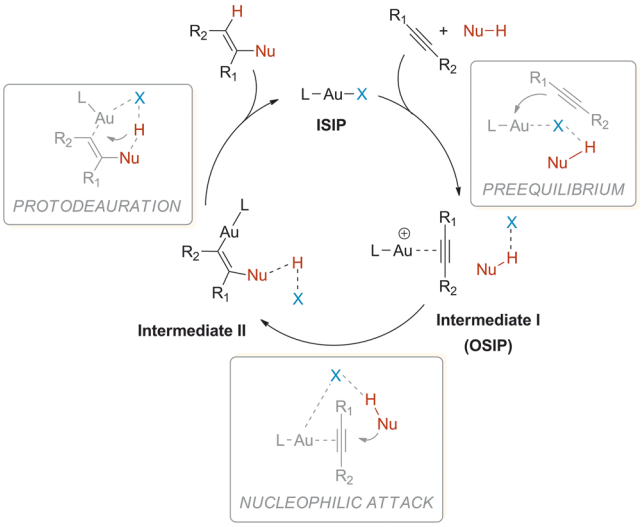
Scheme 1. Proposed Gold Catalytic Cycle

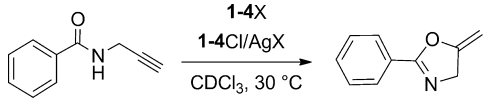


by the anion through the formation of a hydrogen bond. Thus, it is not only a "proton shuttle", as proposed previously.[22]

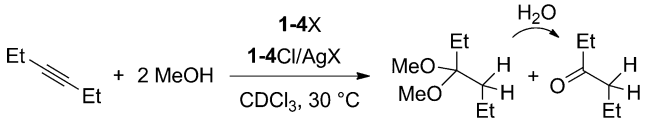
Regardless, both the nature of the ligand[23,24] and counterion effects are considered the two important factors in gold catalysis, but a rational understanding of their synergy/antagonism is still lacking.

For this reason, we synthesized a set of 16 gold complexes of the type L-Au-X (Scheme 2), differing as follows: (i) L = PPh_3 (**L1**), $P(^tBu)_3$ (**L2**), tris(3,5-bis(trifluoromethyl)phenyl)-phosphine (PArF, **L3**), and 1,3-bis(2,6-diisopropylphenyl)-imidazol-2-ylidene (NHC, **L4**), with the deliberate purpose of varying the electron withdrawing ability of the ligand, and (ii) X^- = BF_4^-, OTf^-, OTs^-, and TFA^-, which show various coordinating abilities and basicities.[25] All these complexes were tested as catalysts in two different model reactions: the cycloisomerization of *N*-(prop-2-yn-yl)benzamide to 2-phenyl-5-vinylidene-2-oxazoline (catalysis A, Scheme 3),[26] in which the rate-determining step (RDS) is the protodeauration step,[3] and the methoxylation of 3-hexyne in chloroform (catalysis B, Scheme 4), in which the RDS is the nucleophile attack on the alkyne.[17,19] Thus, we conducted 16 × 2 independent catalytic tests to assess the best/worst ligand/counterion combination, if any, for both catalytic processes.

Scheme 3. Catalysis A, Cycloisomerization of *N*-(Prop-2-ynyl)benzamide to 2-Phenyl-5-vinylidene-2-oxazoline



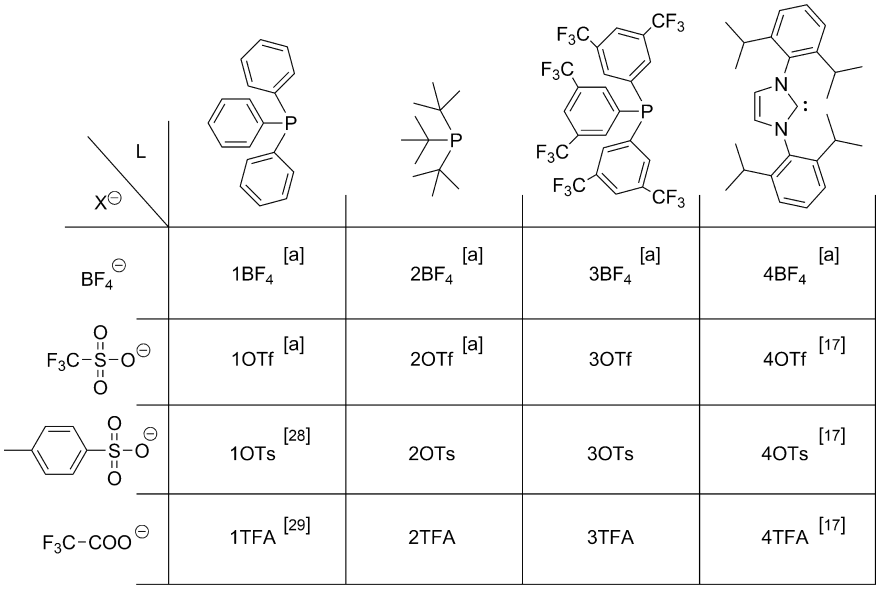
Scheme 4. Catalysis B, Methoxylation of 3-Hexyne in Chloroform



Notably, we have found that the catalytic activity of a given L-Au-X complex is strictly related to the L/X^- combination. In particular, the best settings for catalysis A are PPh_3/OTs^-, $P(^tBu)_3/OTs^-$, and $P(^tBu)_3/TFA^-$, while the worst are PArF/TFA^- and NHC/OTs^-. Furthermore, for catalysis B, superlative combinations are represented by $P(^tBu)_3/OTf^-$ and NHC/OTs^-, while PPh_3/TFA^-, $P(^tBu)_3/TFA^-$, and PArF/TFA^- have been found to be the poorest.

Thus, in fact, the choice of the most efficient L-Au-X catalyst for a given process should not be made by evaluating the properties of L and X^- alone, but rather on the basis of their best combination. Most simply, L and X^- factors must be taken into account together.

Scheme 2. Complete Set of Gold Catalysts Used in This Work[a]



[a]Generated *in situ*.

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RESULTS AND DISCUSSION

Synthesis and Characterization of Gold Catalysts. Neutral compounds **3**,**4**OTf, **1**−**4**OTs, and **1**−**4**TFA (Scheme 2) were synthesized according to a literature procedure (see the Supporting Information for details). Novel complexes **2**OTs, **2**TFA, **3**OTf, **3**OTs, and **3**TFA have been isolated in high yield by reacting **2**Cl or **3**Cl precursors with a slight excess of the appropriate silver salt. All the proton and carbon resonances belonging to the different fragments were assigned via ^{1}H, ^{13}C, ^{19}F, and ^{31}P NMR spectroscopy (see the Supporting Information). With regard to complexes **2**X, the coordination of OTs^- or TFA^- to the $[(\mathbf{L2})Au]^+$ fragment causes a deshielding of the ^{31}P resonance from 96.5 ppm (**2**Cl) to 89.1 ppm (**2**OTs) and 87.4 ppm (**2**TFA). A similar behavior was observed for complexes **3**X; thus, the ^{31}P NMR resonance changes from 36.8 ppm (**3**Cl) to 30.5 ppm (**3**OTf), 32.4 ppm (**3**OTs), and 30.7 ppm (**3**TFA). These variations in the ^{31}P chemical shift with respect to **1**Cl were previously observed for **1**OTf,[27] **1**OTs,[28] and **1**TFA[29] (see the Supporting Information).

Catalysis. All complexes **1**−**4**X (Scheme 2, $X^- = BF_4^-$, OTf^-, OTs^-, and TFA^-) have been tested as catalysts in catalysis A (Scheme 3 and Table 1). The isolated species were employed in the case of all *p*-toluenesulfonates, trifluoroacetates, and **3**−**4**OTf, whereas in all other cases, the catalyst was prepared *in situ* in a NMR tube by mixing equimolar amounts of precursor **1**−**4**Cl and the appropriate silver salt in $CDCl_3$.

Table 1. Gold(I)-Catalyzed Cyclization of *N*-(Prop-2-ynyl)benzamide[a]

entry	catalyst	time (min)	conversion[b] (%)	TOF_i[b,c] (min^{-1})
1	**1**BF_4	114	>98	1.88
2	**2**BF_4	84	>98	1.94
3	**3**BF_4	120	55	1.25
4	**4**BF_4	99	>98	1.86
5	**1**OTf	120	78	1.40
6	**2**OTf	120	83	0.92
7	**3**OTf	120	50	0.74
8	**4**OTf	120	89	1.29
9	**1**OTs	63	>98	4.16
10	**2**OTs	40	>98	3.67
11	**3**OTs	120	53	0.76
12	**4**OTs	120	65	0.84
13	**1**TFA	120	63	1.07
14	**2**TFA	73	>98	3.89
15	**3**TFA	120	22	0.13[d]
16	**4**TFA	120	56	0.54

[a]Catalysis A conditions: 30 °C, *N*-(prop-2-ynyl)benzamide (80 mg, 0.5 mmol), 1 mol % catalyst (or 1:1 L-Au-Cl/AgX) in $CDCl_3$ (500 μL). [b]Conversions and TOF_i determined by ^{1}H NMR spectroscopy as the average of three runs. [c]$TOF_i = (n_{product}/n_{catalyst})$/time (at 30% conversion). [d]To calculate the TOF_i value, the catalytic process was followed until 30% conversion was reached.

A typical catalytic run was performed by mixing *N*-(prop-2-ynyl)benzamide in the presence of 1 mol % catalyst (or 1:1 L-Au-Cl/AgX) at 30 °C in $CDCl_3$. The progress of the reaction was monitored by NMR spectroscopy (see the Supporting Information for details). Quantitative (>98%) conversion of the substrate into 2-phenyl-5-vinylidene-2-oxazoline was reached in 114, 84, and 99 min by using **1**BF_4, **2**BF_4, and **4**BF_4, respectively (Table 1, entries 1, 2, and 4). Much less efficiently, **3**BF_4 promoted the formation of the reaction product in only 55% yield after 120 min (Table 1, entry 3).

By changing the anion from BF_4^- to OTf^-, we observed a slight decrease in the catalytic efficiency for all the catalysts (Table 1, entries 5−8 vs entries 1−4). Again, the complex bearing PArF (**3**OTf) proved to be the less active catalyst within the series **1**−**4**OTf (Table 1, entry 7).

To verify that "silver effects"[30] are negligible under our catalytic conditions, isolated **1**OTf was also employed as catalyst giving similar conversion of **1**Cl/AgOTf (see Table S1 of the Supporting Information)

Using a more basic and coordinating anion such as OTs^-, very different catalytic performances were observed within the series **1**−**4**OTs. Thus, a complete conversion was obtained in the case of **1**OTs and **2**OTs after 63 and 40 min, respectively (Table 1, entries 9 and 10). On the other hand, **3**OTs and **4**OTs gave performances comparable to that of **3**OTf (Table 1, entries 7, 11, and 12). It is worth noting that the catalytic activity of **4**OTs is very similar to that of **3**OTs, while when the anion is BF_4^-, **4**BF_4 shows the same high efficiency of **1**BF_4 and **2**BF_4, different from that of **3**BF_4 (Figure 1).

Finally, in the case of TFA^-, the most coordinating and basic anion of the four screened in this work, generally low catalytic performances were observed, with the exception of **2**TFA, which

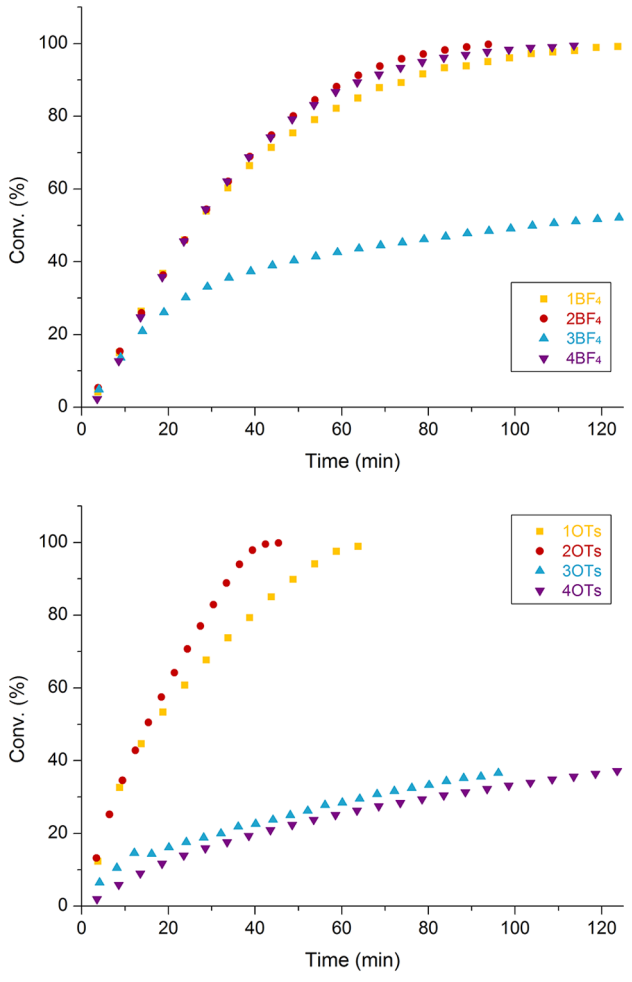

Figure 1. Catalysis A performed by **1**−**4**BF_4 (top) and **1**−**4**OTs (bottom) complexes.

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allows complete formation of 2-phenyl-5-vinylidene-2-oxazoline in a short reaction time.

Comparing the value of the initial turnover frequency, TOF_i (Table 1 and Figure 2), one can see that for catalysts bearing

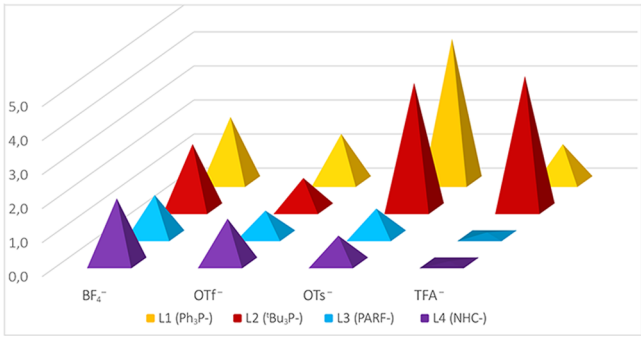

Figure 2. TOF_i values for catalysis A promoted by **1**−**4**X (X^- = BF_4^-, OTf^-, OTs^-, and TFA^-).

triphenylphosphane (Table 1, entries 1, 5, 9, and 13) the best anion is OTs^- followed, in order, by BF_4^-, OTf^-, and TFA^-. The range of TOF_i values varies from 1.07 to 4.16 min^{-1}. With the exception of **2**TFA, an analogous trend can be observed for catalysts **2**X (Table 1, entries 2, 6, and 10). Different from **1**TFA, complex **2**TFA exhibits approximately the same high performance as **2**OTs, their TOF_i values being 3.67 and 3.89 min^{-1}, respectively. By contrast, for **3**X and **4**X series, the catalytic activity decreases following exactly the increasing basicity of the anion. In fact, the TOF_i values are 1.25, 0.74, 0.76, and 0.13 min^{-1} for **3**BF_4, **3**OTf, **3**OTs, and **3**TFA, respectively, and 1.86, 1.29, 0.84, and 0.54 min^{-1} for **4**BF_4, **4**OTf, **4**OTs, and **4**TFA, respectively.

The cycloisomerization of *N*-propargylcarboxamides is a well-studied gold-catalyzed reaction in which protodeauration is considered the slow step (Scheme 1).[3a−d] A pseudo-first-order kinetics with respect to the catalyst concentration is observed,[31] and the key vinyl gold intermediate (Scheme 1, intermediate **II**) has been identified in the case of NHC-Au(I)[26c,d] and PPh_3-Au(I)[2,31] by the groups of Hashmi and Hammond, respectively, and by Ahn[32] and co-workers in the case of gold(III). These observations make us believe that the formation of the vinyl gold complex (intermediate **II**) is not the rate-determining step.

In intermediate **II**, the gold−carbon bond is cleaved by a proton (protodeauration, RDS) to give the final product and regenerate the catalyst (Scheme 1, ISIP). Accordingly, it was found that the additives that are good hydrogen bond acceptors increase the efficiency of this reaction, because they can act as a proton shuttle.[33]

To confirm that the organogold intermediate is actually present in our catalytic mixture, ^{31}P NMR spectra have been recorded during the catalysis for complexes **1**−**3**X (X^- = BF_4^-, OTf^-, OTs^-, and TFA^-). ^{31}P NMR monitoring indicated that the resting state for the gold catalyst is a vinyl gold complex, intermediate **II**. At high conversions, also the coordination of the product is observed (see the Supporting Information for details). Therefore, it is reasonable to assume that the protodeauration step is slow, and consequently, it is the RDS for all **1**−**4**X catalysts under our reaction conditions (Table 1).

In the literature, it is suggested that two important factors should be taken into account to rationalize the activity of L-Au-X compounds: (i) the breaking of the Au−C bond, which is related to the nature of the ligand L,[2,34] and (ii) the ability of the counterion to promote the proton shuttle,[22] which is related to the acid−base nature[35] and hydrogen bond acceptor powers of X^-.[33]

With regard to the first point, if we compare the results obtained using **1**−**4**BF_4 catalysts (BF_4^- is a poor basic and noncoordinating anion[36]) we observe that compound **3**BF_4, bearing the most electron-withdrawing ligand (PArF), is by far the worst catalyst within the series (Table 1, entry 3 vs entries 1, 2, and 4), presumably because it renders the Au−C bond more stable.[3] On the other hand, **1**BF_4, **2**BF_4, and **4**BF_4 showed higher activity, but with almost negligible differences in their performance.[37]

To verify the importance of the acid−base nature and hydrogen bond acceptor powers of the counterion (second point), we can consider the series of complexes **4**X (X^- = BF_4^-, OTf^-, OTs^-, and TFA^-). It can be seen that the catalyst activity is related to the basic strength of the anion (Table 1, entries 4, 8, 12, and 16). Performances of the catalysts decrease gradually with the increasing basicity and hydrogen bond acceptor power of X^- (basic strength: $BF_4^- < OTf^- < OTs^- < TFA^-$). The plausible scenario for **4**X is that anions that are too basic with higher hydrogen bond acceptor powers (OTs^- and TFA^-) do not easily release the proton to gold, thus slowing the reaction rate.

In the case of phosphane complexes **1**−**2**X (X^- = OTf^-, OTs^-, and TFA^-), the catalytic activity of each compound follows the basicity scale of X^-, and medium to highly basic and hydrogen bond acceptor OTs^- and TFA^- anions give better results (Table 1, entries 9, 10, 13, and 14).

A possible explanation can be found in the coordination properties (affinity) of medium to highly coordinative OTs^- and TFA^- anions toward Au.[38]

In the case of complexes **1**X and **2**X, the best anions are by far OTs^- and TFA^-, respectively, probably because during the proton shuttle the anion can interact with the Au atom. This interaction weakens both Au−C and H−X bonds simultaneously, accelerating the reaction (Scheme 1, protodeauration). A similar trend was recently observed by Xu and Hammond.[33] They observed that the addition of NaOTs or HCOONa to a catalytic chloroform solution of **1**OTf and *N*-propargylcarboxamides enhances the catalytic performance 3.9- and 1.4-fold, respectively. Unlike OTs^-, there are not many examples in gold catalysis in which TFA^- becomes the best choice.[11d]

Finally, the behavior of **3**X is similar to that of the related NHC complexes (**4**X). In this case, the interionic structure of OSIP [PArF-Au-(2-hexyne)BF_4] shows that the anion has a strong tendency to interact with the highly positively charged *ortho* proton of the aryl fragment (3,5-CF_3-C_6H_3) rather than with the gold atom.[14b] This evidence suggests that Au···X interaction is less probable during protodeauration.

On the basis of all these observations, a general trend can be drawn as follows. When the coordination of the anion to gold during the protodeauration step (Scheme 1) is not favored, the catalytic performances follow the basicity of the anion. This is the case for complexes **3**X and **4**X (Figure 2). As a confirmation, the interionic structure of NHC-Au(3-hexyne)BF_4 OSIP, determined by a $^{19}F-^1H$ HOESY experiment and explained by the DFT calculation of Coulomb potential, suggests that the counterion does not easily interact with the gold fragment.[14d] On the other hand, when coordinated of X^- to gold is possible, a balance between basicity and hydrogen bond acceptor power versus coordination ability of the anion is observed. This is the case for complexes **1**X and **2**X, where the ion pair structures of

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strictly related compounds **L1**-Au-(η^2-Me-styrene)BF_4 and **L2**-Au-(η^2-3-hexyne)BF_4 suggest that the counterion can interact with the gold atom.[14a,e]

The results presented here show that the anion properties, both coordination ability and basicity (hydrogen-bond acceptor power), have a great impact on the "proton shuttle ability"[22] of the counterion, and more importantly, this ability depends on the ligand L present in the cationic gold fragment.

In summary, the catalytic results obtained studying the gold-catalyzed cycloisomerization of *N*-(prop-2-ynyl)benzamide show that ligands with weaker electron withdrawing ability generally accelerate the reaction, but the exact order cannot be trivially anticipated because of the match/mismatch of ligand and anion properties. Taking into account the most used catalysts **1**X and **4**X, we can conclude that the intermediate coordinating ability and hydrogen bond power of OTs^- provide the best results within the **1**X series (PPh_3 ligand), while BF_4^- or OTf^- is the best choice for the **4**X series (NHC ligand).

Very recently, we[17] and others[19] found a complete inverse trend for the intermolecular alkoxylation of 3-hexyne with methanol: whereas OTf^- is the best compromise for PPh_3, OTs^- is the most suitable anion for NHC-containing catalysts. To complete and rationalize these findings, complexes **1**−**3**X (Scheme 2) have been tested as catalysts in catalysis B (Scheme 4 and Table 2) under the same experimental conditions described previously.[17] A typical catalytic run was performed by mixing 3-hexyne and methanol in the presence of the active catalyst (X^- = OTs^- and TFA^-) or the catalyst precursor **1**−**3**Cl and the appropriate silver salt (X^- = BF_4^- and OTf^-), at 30 °C in $CDCl_3$. In Table 2, the already published results[17] concerning complexes **4**X have been added for useful comparison.

Table 2. Gold(I)-Catalyzed Methoxylation of 3-Hexyne in Chloroform

entry	catalyst	time (min)	conversion[b] (%)	TOF_i[b,c] (min^{-1})
1	**1**BF_4	120	36	0.31
2	**2**BF_4	118	>98	2.72
3	**3**BF_4	120	>98	1.43
4	**4**BF_4	42	>98	2.86[17]
5	**1**OTf	120	84	0.97
6	**2**OTf	61	>98	5.84
7	**3**OTf	52	>98	3.45
8	**4**OTf	33	>98	3.46[17]
9	**1**OTs	120	70	0.69
10	**2**OTs	120	82	2.43
11	**3**OTs	120	94	2.37
12	**4**OTs	18	>98	5.06[17]
13	**1**TFA	120	5	0.05[d]
14	**2**TFA	120	4	0.04[d]
15	**3**TFA	120	1	0.03[d]
16	**4**TFA	120	72	0.60[17]

[a]Catalysis B conditions: 30 °C, 3-hexyne (100 μL, 0.88 mmol), 1 mol % catalyst (or 1:1 L-Au-Cl/AgX), CH_3OH (143 μL, 4 equiv), in $CDCl_3$ (400 μL). [b]Conversions and TOF_i determined by ^1H NMR spectroscopy as the average of three runs. [c]TOF_i = ($n_{product}/n_{catalyst}$)/time (at 30% conversion). [d]To calculate the TOF_i value, the catalytic process was followed until 30% conversion was reached.

This reaction occurs at room temperature and can be conveniently monitored by NMR spectroscopy (see the Supporting Information for details). Under these conditions, it is known that the enol−ether intermediate, resulting from the first attack of methanol on 3-hexyne, is very reactive and quickly undergoes the attack of a second molecule of methanol, leading to the formation of 3,3-dimethoxyhexane. It should be noted also that 3-hexanone, arising from 3,3-dimethoxyhexane hydrolysis due to traces of water, was detected in solution.

Complexes **2**BF_4 and **3**BF_4 promoted full conversion of the precursors within 120 min (Table 2, entries 2 and 3), whereas catalyst **1**BF_4 in the same reaction time promoted only 36% conversion (Table 2, entry 1).

When the catalytic process was conducted using **1**−**3**OTf as the catalysts, an overall neat increase in the reaction rate was observed. Again, the complex bearing PPh_3 (**1**OTf) gave the poorest result, as only 84% conversion was reached within 120 min. By contrast, the reaction catalyzed by **2**OTf and **3**OTf reached full conversion in 61 and 52 min, respectively (Table 2, entries 5−7).

When OTf^- is replaced with a more coordinating and basic anion such as OTs^-, lower activity was exhibited by all catalysts (**1**−**3**OTs). Thus, 70, 82, and 94% conversions were recorded for **1**OTs, **2**OTs, and **3**OTs, respectively, after a reaction time of 120 min (Table 2, entries 9−11, respectively).

Finally, using TFA^- as a counterion, the reaction rate for all catalysts **1**−**3**TFA slowed further, and only small amounts of product (≤5%) were detected after 120 min (Table 2, entries 13−15).

Comparing the values of initial turnover frequency TOF_i (Table 2 and Figure 3), one can observe that all complexes bearing phosphanes (**1**−**3**X) follow the same trend, although with different magnitudes. While only a slight difference has been observed upon replacement of BF_4^- with OTs^-, OTf^- derivatives showed a 2−3-fold increase in catalytic activity. **1**−**3**TFA are the worst catalysts, as judged by their extremely low TOF_i values. On the other hand, complexes **4**X follow a different trend,[17] as the performance increases upon going from BF_4^- to OTf^- and then to OTs^-, but it finally collapses in the case of TFA^- (entries 4, 8, 12, and 16 in Table 2 and Figure 3).

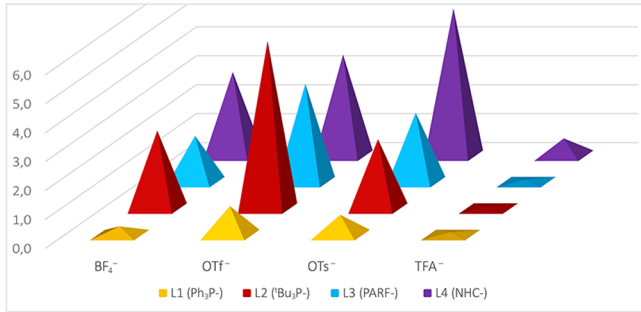

Figure 3. TOF_i values for catalysis B promoted by **1**−**4**X (X^- = BF_4^-, OTf^-, OTs^-, and TFA^-).

The alkoxylation of alkynes has been deeply studied by several groups,[39] and the accepted mechanism is shown in Scheme 1. In the presence of certain phosphanes, the formation of the gem-diaurated species[40] was observed, which causes a different kinetic profile of the reaction for different L ligands. The detailed study of the kinetic profile has led to the conclusion that, in the catalytic cycle, only one gold atom is involved and that the RDS of the reaction is the attack of methanol on the ISIP (Scheme 1) for both phosphane and NHC ligands.[17,19] A notable anion effect was observed, particularly in the initial steps of the reaction: pre-

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equilibrium ISIP−OSIP and activation of methanol during the nucleophile attack (Scheme 1).[17,19]

In the nucleophilic attack step, the anion acts as a template, holding the methanol in the right position for the outer sphere attack and as a hydrogen bond acceptor, improving the nucleophilicity of the attacking methanol.

In particular for NHC complexes, the intermediate coordinating ability and basicity of OTs^- afford the best compromise for achieving an efficient catalyst. Thus, in the presence of this anion, the pre-equilibrium is shifted toward the OSIP and its characteristic basicity promotes the nucleophilic attack (much better than less basic $BArF^-$ {tetrakis[3,5-bis(trifluoromethyl)-phenyl]borate}, BF_4^-, and OTf^- anions). With regard to **1**X, it has been found that OTf^- is the best anion, and it has been suggested that OTs^- is too coordinating to $\mathbf{1}^+$, reducing the amount of OSIP in solution.[19]

Via analysis of our results, it should be noted that for all **1**−**4**X complexes the catalytic performances improve upon replacement of BF_4^- with OTf^-, as expected, because of the higher basicity and hydrogen bond acceptor powers of the latter. However, if the basicity of the anion is further increased (OTs^-), opposite trends in the function of the ligand L can be observed. Thus, while a decrease in catalytic efficiency was measured for all species bearing phosphanes (**1**−**3**), a significant increase was obtained for NHC.

To understand these differences, at first we deeply investigated the ISIP−OSIP equilibrium (Scheme 1) during the reaction, recording ^{31}P NMR spectra at different reaction times. We found that OTs^- tends to re-enter gradually in the first coordination sphere of gold (ISIP) while the reaction proceeds and the amount of alkyne and methanol is decreasing (Figure 4 and the Supporting Information). We can ascribe the different catalytic behavior observed for **1**−**3**OTs, with respect to that of **4**OTs, to the higher coordination power of OTs^- when phosphanes rather than NHC are bound to gold. However, it is also possible that OTs^- shows a different ability to act as a template (holding the methanol for the outer sphere attack and as a hydrogen bond acceptor) when NHC is replaced with phosphanes.

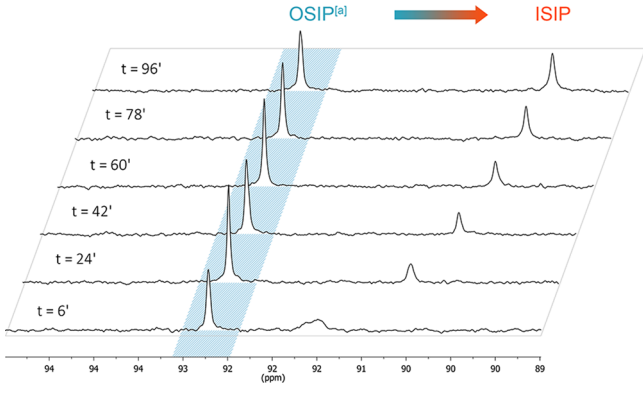

Figure 4. ^{31}P NMR spectra recorded at different reaction times for catalysis B conducted with **2**OTs. [a] and/or gem-diaurated.[39a]

Finally, the very strong tendency of TFA^- to coordinate to gold and its high basicity deeply undermine catalyst efficiency for all species bearing phosphanes (**1**−**3**), preventing alkyne coordination and forming free MeO^- in solution, which poisons the catalyst (Supporting Information) as observed for **4**X.[17,18]

CONCLUSION

From the results reported here, it is evident that the correct choice of the ligand L, to improve the performances of L-Au-X complexes in catalysis, strongly depends on the nature of the anion X^- and vice versa.

For NHC compounds, noncoordinating and weakly basic anions (such as BF_4^-) may be the best choice for a reaction in which the RDS is protodeauration, as in the case of the cycloisomerization of *N*-propargylcarboxamides. On the other side, the intermediate coordinating ability, basicity, and hydrogen bond acceptor property of OTs^- provide the best compromise for achieving an efficient catalyst in the methoxylation of 3-hexyne, where the RDS is the nucleophilic attack helped by the counterion. In the case of complexes bearing phosphanes, a completely different behavior has been outlined. Thus, an intermediate to high coordination ability of the anion combined with its relatively high basicity and hydrogen bond acceptor property (OTs^- and TFA^-) has been found to accelerate the cycloisomerization of *N*-(prop-2-ynyl)benzamide. Instead, a medium to low coordination power and a weak basicity of the anion (BF_4^- and OTf^-) are suitable for the methoxylation of 3-hexyne. A possible explanation can be found in the higher affinity of the counterion (especially OTs^-) for the gold fragment when the ancillary ligand L is a phosphane with respect to NHC: a higher gold affinity accelerates the reaction in which the RDS is the protodeauration but inhibits it when the RDS is the nucleophilic attack, because of the shift of the ISIP−OSIP equilibrium (Scheme 1) in favor of ISIP.

This study clearly demonstrates that the interplay between the ligand nature and anion effect is crucial in different steps of the catalytic cycle. The multiple roles played by counterions and L-Au^+ fragments in chemical transformations require more comprehensive computational and experimental studies of the ligand/anion correlation. These studies are underway in our laboratories.

ASSOCIATED CONTENT

Supporting Information

General procedures and materials, synthesis and characterization of novel compounds, catalysis plot, and ^{31}P NMR spectra of **1**−**3**X for catalysis A and catalysis B. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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